Given these low odds, it is far more reasonable to expect the person of ordinary skill to pursue one of a number of other safer solutions then available to develop a longer-acting compound. These other solutions included controlled (or extended) release. Abraham Tr. 392:9-23; Wolff Tr. 649:8-16; Meltzer Tr. 282:10-12. By making a controlled or extended release formulation, one would use the same compound, thus avoiding the uncertain risk associated with compound modification.

A number of technologies existed in March 1985 for making controlled or extended release products: persons of ordinary skill in the art could develop a depot (long lasting) injection, a controlled release capsule (such as Contac) or a transdermal patch. Abraham Tr. 392:11-23; Wolff Tr. 649: 8-16; Meltzer Tr. 282:10-12.

Defendants do not dispute the availability of these other solutions. Moreover, Defendants offered no testimony to explain why one of ordinary skill in the art would not pursue these solutions, instead of modifying pirenperone.

(2) <u>It Would Not Have Been Obvious to Replace the Ketone With a Benzisoxazole</u>

If the person of ordinary skill in the art wanted to modify pirenperone, he or she would have looked to the most common methods of altering a molecule:

classical isosteric replacements.

Classical isosteric replacement follows Grimm's hydride displacement law. Abraham Tr. 370:12-371:2. Standard isosteric replacements for ketones were available and well-known in and prior to 1985. Abraham Tr. 372:2-6, 372:15-24, 394:20-395:18; Wolff Tr. 658:2-6. These standard replacements, when applied to pirenperone, would have resulted in changes well-recognized in the prior art, Strupczewski Dep. (11/16/2004) Tr. 155:8-24, and in standard textbooks, PX 141 at 75, PX 158 at 3151.

One of ordinary skill in the art would choose one of these standard replacements, not the replacement of a ketone with benzisoxazole. Abraham Tr. 395:24-396:11. Defendants' experts provided no testimony – let alone clear and convincing evidence – why these standard replacements would not be pursued first.

Alternatively, one could make "non-classical bioisosteric" replacements. Abraham Tr. 369:7-24. A bioisosteric replacement is a change that is believed to act with the same biological system. Such changes are much riskier than classical isosteric replacements. There is no guarantee that the changed compound will have the same activity as the original compound. Rather, the changed chemical compound could have the same activity, the opposite activity, or no activity at all.

Abraham Tr. 369:25-370:10; PX 141 at 73.

There are numerous problems with bioisosteric replacement as an approach to drug modification. First, there was no reasonable expectation in 1985 that bioisosteric replacement would work. Abraham Tr. 374:3-8.

Second, there was no reasonable expectation in 1985 that bioisosteres would bind to the same receptor. Abraham Tr. 374:10-13.

Third, for bioisosteric replacements there are different degrees of binding even to the same receptor. Abraham Tr. 375:14-17. Or activity on the same receptor can be opposite after a bioisosteric change, such that one chemical compound is an agonist and a compound that is a bioisostere is an antagonist. Abraham Tr. 377:9-19.

Fourth, bioisosteric replacement can also cause issues with absorption, distribution, metabolism, and excretion ("ADME"). Abraham Tr. 377:20-379:6; 379:11-14. These ADME issues can come into play as soon as the drug is given, while the drug is on the receptor, or after it is on the receptor. Abraham Tr. 379:20-25.

Fifth, bioisosteric replacement can cause different results in different animals. Abraham Tr. 380:2-5.

Sixth, even knowing the three-dimensional structure of receptors, one

cannot predict which bioisosteres will be active. Abraham Tr. 381:11-14.

Defendants' experts did not offer evidence that contradicted Professor Abraham's testimony on these problems that generally occur with bioisosteric replacement.

Notwithstanding these problems, there were in 1985 a few known and recognized bioisosteric replacements. Abraham Tr. 394:20-396:11, 425:10-426:7. Defendants ignore these recognized replacements and insist that it was obvious to use an unrecognized non-classical bioisosteric replacement, one that just happens to be the only replacement that modifies pirenperone to arrive at Defendants' desired result, compound 11. Such a decision is not based on the science; it is the result of inappropriate hindsight.

Defendants propose replacing the ketone with a benzisoxazole, a modification that requires that two extra atoms be added, and that a new ring be formed, to transform pirenperone into compound 11. Abraham Tr. 429:13-22.

As of March 1985, this substitution was not recognized in the art. Abraham Tr. 396:12-17. As of 1985, the benzisoxazole-for-ketone swap appeared in no standard reference as a bioisosteric replacement. Wolff Tr. 659:16-23, 661:8-12.

Instead of looking in standard texts, Mylan and DRL rely on inferences from publications that say nothing about bioisosteric replacement, most of which

do not even involve antipsychotics. None of the cited literature describes benzisoxazole as a bioisosteric replacement for a ketone. Instead, Defendants merely infer it. Wolff Tr. 664:1-4, 667:9-16.

In fact, a person of ordinary skill would consider none of the cited references because (1) they do not discuss bioisosteric replacements, (2) they do not address the problem Defendants identify of making a compound longer-lasting, and/or (3) they are from the wrong field.

Defendants principally rely on the Strupczewski work at Aventis (then Hoechst-Roussel Pharmaceuticals). This work included an abstract, PX 191, and the '811 patent, PX 81. These references simply reported Hoechst's work on antipsychotic compounds. There is not a word in these references about modifying the structures disclosed in them. Wolff Tr. 662:9-11, 663:9-15, 16-25; Abraham Tr. 398:1-15; PX 191; PX 81.

The other references cited by Defendants, the Saunders article, PX 195, and Shutske article, PX 192, are even less relevant. Those articles do not relate to antipsychotics. Abraham Tr. 396:21-25; Wolff Tr. 665:2-7. Instead, Shutske, PX 192, is about diuretics and Saunders, PX 195, concerns anti-inflammatory agents. Janssen argues that Saunders and Shutske are non-analogous references and thus, are not relevant. See e.g., Litton Sys., Inc. v. Honeywell, Inc., 87 F.3d 1559, 1568

(Fed. Cir. 1996).

The Court need not decide this question because even assuming these articles are analogous prior art, they still would not direct the person having ordinary skill in the art to make the change Mylan and DRL propose. As with the Strupczewski work, Saunders and Shutske, PX 195 and PX 192, contain no discussion on bioisosterism. Abraham Tr. 397:15-25; Wolff Tr. 664:21-23. Nor do they talk about benzisoxazoles being a bioisosteric replacement for a ketone. Wolff Tr. 664:24-665:1.

As stated earlier, when a chemical compound is at issue, "a prima facie case of obviousness requires 'structural similarity between claimed and prior art subject matter . . . where the prior art gives reason or motivation to make the claimed compositions.'" Yamanouchi, 231 F.3d at 1343 (quoting Dillon, 919 F.2d at 692). Mylan and DRL have failed to demonstrate that the prior art would have motivated the person of ordinary skill in the art in 1985, with no knowledge of the '663 patent, to (1) choose pirenperone as his or her lead compound, (2) determine that pirenperone was deficient due to its alleged short duration, (3) determine that this problem was due to metabolism of a ketone, and (4) determine that this problem could be solved by replacing the ketone with a benzisoxisole with any kind of reasonable expectation of success. Accordingly, Defendants have failed to present

a prima facie case of obviousness.

4. Secondary Considerations: Objective Evidence of Nonobviousness

An obviousness analysis requires a Court to also examine objective evidence of nonobviousness in the record. Graham, 383 U.S. at 17-18; Ruiz v. A.B. Chance Co., 234 F.3d 654, 667 (Fed. Cir. 2000). Such objective evidence includes, *inter alia*, commercial success, long felt, but unsolved need, the failure of others, copying, and unexpected results. Graham, 383 U.S. at 17-18; Ruiz, 234 F.3d at 662-63, 667.

Defendants insist that there is no need for them to refute the secondary considerations with respect to risperidone. Rather, Defendants insist that they can focus their obviousness case solely on compound 11.

This is legally incorrect. The fact that risperidone was chosen for further commercialization while compound 11 was left as a back-up drug does not mean that evidence regarding risperidone's commercial success is irrelevant. It is entirely appropriate, as the Federal Circuit has held, for the patent owner to point to secondary considerations with respect to any commercial embodiment of the claim. Applied Materials, Inc. v. Advanced Semiconductor Materials Am., Inc., 98 F.3d 1563, 1570 (Fed. Cir. 1996); see also See Jackson Jordan, Inc. v. Plasser

Am. Corp., 747 F.2d 1567, 1578 (Fed. Cir. 1984) ("The claims [of a patent], not particular embodiments, must be the focus of the obviousness inquiry.").

Both parties agree that the commercial embodiment of the '663 patent, Risperdal, is risperidone and is encompassed by each and every claim of the ' 663 patent in addition to compound 11. SF 17. Thus, secondary considerations with respect to risperidone are relevant here.

Objective evidence of nonobviousness "may often be the most probative and cogent evidence in the record." Stratoflex Inc. v. Aeroquip Corp., 713 F.2d 1530, 1538 (Fed Cir. 1983). Indeed, secondary considerations "may be sufficient to overcome a prima facie case of obviousness." In re Beattie, 974 F.2d 1309, 1313 (Fed. Cir. 1992). Of course, here, Mylan and DRL have failed to make out a prima facie case. Nevertheless, the Court will examine the secondary considerations, as it must.

a. Commercial Success

Commercial success of an invention is evidence that it would not have been obvious. Demaco Corp. v. F. Von Langsdorff Licensing Ltd., 851 F.2d 1387, 1391-92 (Fed. Cir. 1988). Risperidone, sold as Risperdal, is an incredible commercial success. Sales have increased every year since it was first sold in 1994, and it experienced double digit growth in most years. PX 414; PX 730;

Vergis Tr. 77:6-10.

Within three years it became the most prescribed antipsychotic, quickly overtaking clozapine (sold as Clozaril) and haloperidol (sold as Haldol). PX 744; Vergis Tr. 78:17-79:9.

Today, a decade after launch, it is still the second most prescribed antipsychotic. PX 417; PX 673; Vergis Tr. 79:18-80:10; Tamminga Tr. 55:19-56:5; Meltzer Tr. 283:4-22.

Risperdal has been used to treat at least five million people. Meltzer Tr. 283:4-22. Last year, Risperdal was Johnson & Johnson's largest product, accounting for just under $3 billion in worldwide sales. Vergis Tr. 78:9-16.

b. Long Felt, But Unsolved Need

Evidence of a long-felt but unsolved need in the industry for the solution offered by the patented invention supports a finding that the invention would not have been obvious at the time the invention was made. Monarch Knitting Machinery Corp. v. Sulzer Morat GmbH, 139 F.3d 877, 884 (Fed. Cir. 1998). "[L]ong-felt need is analyzed as of the date of an articulated identified problem and evidence of efforts to solve that problem." Texas Instruments Inc. v. ITC, 988 F.2d 1165, 1178 (Fed. Cir. 1993).

In this case it is undisputed that there was a long-felt but unsolved need for

a safe, atypical antipsychotic that did not cause EPS or TD from at least the 1960s until 1985 and beyond. Tamminga Tr. 49:19-50:16, 51:1-52:5; Meltzer Tr. 283:4-22; Wolff Tr. 648:18-20.

The invention and eventual approval of Risperdal solved this long felt, but unfilled need. Risperidone was the first compound available to physicians for general use that safely combined the efficacy of a typical antipsychotic with reduced EPS. Its development "has been very exciting to the medical field." Tamminga Tr. 52:25-53:13, 53:23-54:2; Meltzer Tr. 253:17-20, 254:14-255:9.

c. Failure of Others

Evidence of failed attempts by others supports a finding that the patented invention would not have been obvious. Advanced Display Sys., Inc. v. Kent State Univ., 212 F.3d 1272, 1285 (Fed. Cir. 2000).

From the discovery of clozapine in the late 1960's through 1985, the scientific community was unsuccessful in developing an antipsychotic with reduced EPS for general use. Meltzer Tr. 253:13-16. During that time period, many pharmaceutical companies made such attempts. For example, Dr. McMillen worked with Bristol-Myers to develop an atypical antipsychotic. McMillen Tr. 504:12-25. Yet no approved drug resulted from those years of research.

Many pharmaceutical companies identified promising atypicals, such as

fluperlapine, remoxipride, and serotonyl, that all failed to result in an approved drug – until risperidone. Meltzer Tr. 282:22-283:3.

Most telling is the work of Hoechst-Roussel. Beginning in the 1970s, Hoechst-Roussel had a program to develop improved antipsychotic drugs with reduced EPS. Strupczewski Dep. (11/16/2004) Tr. 101:2-21, 151:2-12, 198:4-199:16.

As part of this program, Hoechst-Roussel developed compounds relied on by Defendants – the Strupczewski '811 patent, PX 81, and abstract, PX 191. Strupczewski Dep. (11/16/2004) Tr. 151:14-152:15, 105:12-23, PX 81, PX 191.

One of the Hoechst-Roussel compounds that Defendants rely on is HRP-913. Hoechst-Roussel filed an Investigational New Drug Application ("IND") with the FDA to conduct clinical trials on HRP-913, but those trials were a failure. Strupczewski Dep. (11/16/2004) Tr. 213:8-24, 188:16-21. HRP-913 caused marked adverse side effects in healthy volunteers on whom it was tested and had little useful therapeutic effect. Strupczewski Dep. (11/16/2004) Tr. 217:24-218:22; Strupczewski Dep. (11/17/2004) Tr. 27:8-18, 28:11-30:2. As a result, Hoechst-Roussel discontinued its development. Strupczewski Dep. (11/17/2004) Tr. 11:10-16, 21:2-13; Meltzer Tr. 252:22-253:12.

Similarly, in the early 1980s, Hoechst-Roussel developed a chemical

compound it called HR 592. Strupczewski Dep. (11/17/2004) Tr. 39:11-23. Hoechst-Roussel believed that HR 592 would have useful antipsychotic properties and the company submitted an IND to investigate HR 592 in humans. Strupczewski Dep. (11/17/2004) Tr. 42:2-21, 47:13-48:10, 50:21-51:11. But, as with HRP-913, HR 592 was not effective against schizophrenia in patients. To the contrary, it exacerbated patients' symptoms, and one patient even committed suicide when administered HR 592. Strupczewski Dep. (11/17/2004) Tr. 61:10-18. 69:24-70:8. As a result, Hoechst-Roussel discontinued development of HR 592. Strupczewski Dep. (11/17/2004) Tr. 73:2-74:7.

To this day, Hoechst-Roussel (now Aventis) has never succeeded in bringing an antipsychotic drug to market. Strupczewski Dep. (11/16/2004) Tr. 108:9-15.

The evidence establishes that there was a failure of others to develop a safe, atypical antipsychotic prior to the time Janssen filed its risperidone patent application.

d. Copying

Copying the patented invention is also evidence that the invention would not have been obvious. Dow Chem. Co. v. American Cyanamid Co., 816 F.2d 617, 622 (Fed. Cir. 1987).

Janssen received certification letters from ten different generic manufacturers that they filed ANDAs with the FDA in order to market generic risperidone products. Vergis Tr. 82:2-15; Meltzer Tr. 283:4-22. There has been undisputed copying of risperidone, a compound covered by the claims of the '663 patent.

e. Respect by the Industry

Respect of the industry for the validity of the patent is also evidence of nonobviousness. E.g., WMS Gaming, Inc. v. Int'l. Gaming Tech., 184 F.3d 1339, 1359 (Fed. Cir. 1999) ("Objective evidence of nonobviousness may include . . . licenses showing industry respect.").

Of the ten companies that have sought permission from the FDA to market a generic risperidone product, six have respected the validity of the '663 patent and have not asked for permission to sell their products before the expiration of the patent. Vergis Tr. 82:9-13; PX 75, PX 76, PX 77, PX 78, PX 85; PX 396.

f. Acclaim

Appreciation of the invention is further evidence that the invention would not have been obvious. E.g., Vulcan Eng'g Co. v. FATA Aluminum, Inc., 278 F.3d 1366, 1373 (Fed. Cir. 2002); In re Piasecki, 745 F.2d 1468, 1473-74 (Fed. Cir. 1984).

Risperdal and its active ingredient risperidone have received numerous awards from the industry. Vergis Tr. 81:2-4. In 1995, Risperdal received the Prix Galien awards in Canada and France. Vergis Tr. 81:5-18. In 1996, Risperdal received the International Prix Galien. The International Prix Galien is the pharmaceutical industry's equivalent to the Nobel Prize. Vergis Tr. 81:5-18; Meltzer Tr. 283:4-22.

And in 2005, Kennis, one of the inventors of the '663 patent, was named a Hero of Chemistry by the American Chemical Society. The Heroes of Chemistry program recognizes "the vital role of industrial chemical scientists and their companies in improving human welfare through successful commercial innovations and products." Kennis received this award "for the development of Risperidal [sic], a standard in the treatment of psychosis, revolutionizing antipsychotic treatments." PX 309; Vergis Tr. 81:5-82:1.

Additionally, Risperdal has had a tremendous effect on the patients who have taken it, and their families. Risperdal gets schizophrenic patients back into the work place and allows them to reintegrate themselves into their families and society. Ken Steele authored a memoir, The Day the Voices Stopped, PX 68, in which he describes his struggle with schizophrenia and the dramatic impact Risperdal had on his life. Vergis Tr. 84:22-85:24; Tamminga Tr. 54:6-55:18. See

also PX 67 at 381.

g. Unexpected Results

The final relevant secondary consideration is unexpected results. Unexpected superior properties of an invention support the conclusion that the invention was not obvious to one of ordinary skill in the art. Knoll Pharm. Co. v. Teva Pharms. USA, Inc., 367 F.3d 1381, 1385 (Fed. Cir. 2004). In making this determination, the Court should look at the evidence from both before and after the patent application was filed. Id.

Risperidone was the first antipsychotic drug available for general use whose antipsychotic activity was equivalent to a typical antipsychotic but that did not cause significant EPS. Meltzer Tr. 253:17-254:9.

Risperidone had a number of unexpected benefits: (1) cognitive improvements, (2) improvement in negative symptoms, (3) reduction in tardive dyskinesia and (4) less metabolic side effects. Typical antipsychotic drugs either did not improve the cognition of schizophrenic patients or they made it worse. They also did not improve the negative symptoms of schizophrenia (social withdrawal, lack of motivation). By contrast, risperidone improved the cognition of schizophrenic patients. It also showed modest improvement of negative symptoms and did not have the disabling sedation of typical antipsychotic drugs.

In addition, risperidone reduced both the frequency of tardive dyskinesia and its symptoms. Also, after subsequent atypical antipsychotic drugs were developed, it was discovered that they cause weight gain and increase the risk of diabetes and cardiovascular disease. Risperidone, by contrast, produces minimal side effects of this kind. Meltzer Tr. 254:14-255:9; PX 46; PX 50; PX 51; PX 54.

5. Defendants Have Failed to Prove Obviousness of the '663 Patent

In sum, Mylan and DRL have failed to demonstrate that the prior art gave reason or motivation to one of ordinary skill in the art to create the claimed compositions. In addition, the secondary considerations overwhelmingly demonstrate the nonobviousness of the '663 patent. Mylan and DRL have therefore failed to meet their burden of proving by clear and convincing evidence that the '663 patent is obvious under 35 U.S.C. § 103(a).

IV. Inequitable Conduct

"Patent applicants and those substantively involved in the preparation or prosecution of a patent application owe a 'duty of candor and good faith' to the PTO." M. Eagles Tool Warehouse, Inc. v. Fisher Tooling Co., 439 F.3d 1335, 1339 (Fed. Cir. 2006) (quoting 37 C.F.R. § 1.56(a) (2004)). Breaching this duty can constitute "inequitable conduct," which renders the patent unenforceable. Id.

at 1340.

There are three steps in the inequitable conduct analysis. See Hoffmann-La Roche, Inc. v. Promega Corp., 323 F.3d 1354, 1359 (Fed Cir. 2003). First, there must have been a "misrepresentation or omission of a material fact." Id. Second, the misrepresentation or omission must have been made "with an intent to deceive the PTO." Id. Materiality and intent to deceive must be shown by clear and convincing evidence. Id. Third, assuming the first two requirements have been met, "the district court must determine whether the equities warrant a conclusion that the patentee has engaged in inequitable conduct." Id. (citing Molins PLC v. Textron, Inc., 48 F.3d 1172, 1178 (Fed. Cir. 1995).[15]

Mylan[16] argues that Janssen withheld material information concerning the dopamine antagonism of pirenperone from the PTO during its prosecution of the '663 patent, and that it did so intentionally. Mylan's arguments focus on the representations made by Janssen patent attorney Geoffrey Dellenbaugh, who

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[15] See also Kemin Foods, L.C. v. Pigmentos Vegetales Del Centro, Nos. 05-1479, 1480, 06-1002, 2006 U.S. App. LEXIS 24246, at *12 (Fed. Cir. Sept. 25, 2006) ("Even when a court finds that the patentee failed to disclose material information to the PTO and acted with deceptive intent, the court retains discretion to decide whether the patentee's conduct is sufficiently culpable to render the patent unenforceable.").

[16] DRL does not join Mylan in alleging Janssen engaged in inequitable conduct.

prosecuted the '663 patent, CEO Paul Janssen, and scientist Dr. Frans Awouters.

A. Materiality

Under the regulations in place during prosecution of the '663 patent, "information is material where there is a substantial likelihood that a reasonable patent examiner would consider it important in deciding whether to allow the application to issue as a patent." 37 C.F.R. § 1.56(a) (1984). This is often referred to as "the Rule 56 standard." Dayco Prods., Inc. v. Total Containment, Inc., 329 F.3d 1358, 1363-64 (Fed. Cir. 2003); Digital Control, Inc. v. Charles Mach. Works, 437 F.3d 1309, 1313-19 (Fed. Cir. 2006).

Materiality does not require that any withheld information, if it had been provided, would have resulted in a rejection of the patent claims by the patent examiner. On the contrary, information can be "material" even if a patent examiner would find the claimed invention to be patentable after considering such information. See Digital Control Inc. v. Charles Machine Works, 437 F.3d 1309, 1313-19 (Fed. Cir. 2006).

Mylan claims that prior art regarding the dopamine antagonism of pirenperone was material information that Janssen failed to disclose to the PTO during the '663 patent prosecution. While the '870 patent for pirenperone was disclosed to the PTO, it only discloses pirenperone's activity as a serotonin

antagonist. PX 80, Dellenbaugh Tr. 138:9-19. Specifically, Mylan points to seven prior art papers, three of which were co-authored by Dr. Janssen, and one which was co-authored by Dr. Awouters. These papers allegedly disclose pirenperone's effectiveness as a dopamine antagonist. DX 86, 89, 112, 120. Among these references are the results of Janssen's clinical trials of pirenperone performed in humans. DX 116, 102.

Mylan's assertion that pirenperone's dopamine antagonism was material rests on communications between Janssen and the PTO during the '663 patent's prosecution. The PTO initially rejected the claims of the application as obvious over U.S. Patent No. 4,335,127 ("the '127 patent" or "the Vandenberk patent"), PX 223, which disclosed a Janssen compound called ketanserin, in view of U.S. Patent No. 4,352,811 ("the '811 patent" or "the Strupczewski patent"), a patent owned by Hoechst-Roussel, PX 81. PX 2 at 113; Dellenbaugh Tr. 129:15-20. The examiner claimed that it would have been obvious to combine the two in order to produce a compound within the claims of the pending application. Dellenbaugh Tr. 163:9-19, DX 173. Dellenbaugh, on behalf of Janssen, replied that a motivation to combine would not exist with respect to the Vandenberk patent because the compounds claimed therein did not possess antipsychotic activity. Dellenbaugh Tr. 165:21-25; DX 176, at 4-5. Dellenbaugh claimed that

this was so, in part, because ketanserin "does not antagonize apomorphine[17]-induced agitation in rats . . . as do the compounds claimed" in the application that would eventually become the '663 patent. DX 176, at 5-6; see also DX 178, at 1.

Additionally, Janssen submitted a declaration by Dr. Awouters comparing ketanserin's apomorphine test results with those of risperidone. DX 178. Janssen's submissions apparently satisfied the PTO, as it passed its application to issue, resulting in the '663 patent. PX 2. Mylan claims this interaction demonstrates the materiality of dopamine antagonism.

It is clear however, that the material issue for the examiner in the above correspondence was antipsychotic activity, not dopamine antagonism per se. The PTO's initial rejection of Janssen's application rested on its belief that the compounds of the '127 and '811 patents had antipsychotic activity: "Since the compounds of both the above references have 'antipsychotic' activity it would not be unreasonable to expect the product to also possess 'antipsychotic' activity." PX 2 at 114; Dellenbaugh Tr. 129:21-130:8. The PTO made no mention of pirenperone or dopamine antagonism. Dellenbaugh Tr. 130:9-11.

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[17] Apomorphine is used in testing as a surrogate for dopamine because it is more chemically stable, but will still bind to dopamine receptors. Thus, a test compound that functions to inhibit the ability of apomorphine to bind to a dopamine receptor will also inhibit the ability of dopamine to bind to that same receptor, i.e., it will function as a dopamine antagonist. Wolff Tr. 543:2-544:13.

Dellenbaugh's response focused on Janssen's belief that the compounds in the '127 patent were not antipsychotics, PX 2 at 123-24, and submitted the data contained in the Awouters declaration to corroborate this claim. PX 2 at 187; see also PX 2 at 195-197.

While it is true that this data relied on ketanserin's lack of dopamine antagonism to support this conclusion, dopamine antagonism with regard to pirenperone was not similarly relevant because pirenperone is demonstrably not an antipsychotic in humans.

As the examiner knew from the pirenperone patent itself, pirenperone was not claimed to be an antipsychotic compound. PX 80.

Defendants rely solely on the fact that pirenperone is a dopamine antagonist for their argument that pirenperone is an antipsychotic. But, as Dr. Meltzer testified, being a dopamine antagonist does not mean that a compound will be an antipsychotic. Instead, there are many reasons why a compound could act as a dopamine antagonist and not be an antipsychotic. Meltzer Tr. 275:25-276:17. It is for that reason that companies such as Janssen developed, used, and published additional tests to determine whether a compound would be an antipsychotic. Meltzer Tr. 271:18-272:19.

Janssen tested pirenperone with these additional tests. The studies and their

published results demonstrated that pirenperone, in contrast to setoperone, was not effective as an antipsychotic. Meltzer Tr. 271:18-272:19, 273:12-275:5; McMillen Tr. 509:16-510:22; PX 94/DX 141; PX 388; PX 389.

Pirenperone had failed two standard tests for antipsychotics, it was being studied in humans for anti-anxiety, not as an antipsychotic, and it was reported in the literature not to be an antipsychotic. Wolff Tr. 638:23-639:5, 641:6-8, 641:18-20; McMillen Tr. 511:8-10; Meltzer Tr. 269:5-8; PX 22; PX 94; PX 96; PX 202; PX 388; PX 389.

Far from supporting any theory of obviousness, disclosure of more information about pirenperone would only have further demonstrated its lack of materiality. The additional pirenperone information teaches away from the invention, not towards it. Halliburton, 925 F.2d at 1441 (finding information in reference that taught away from the invention non-material).

Mylan has failed to present clear and convincing evidence that prior art regarding pirenperone's dopamine antagonism was material.

B. Intent to Deceive

Even if there were a material omission, there is no clear and convincing evidence that anyone acted with an intent to deceive the PTO. Without an intent to deceive, there can be no inequitable conduct. Kingsdown Med. Consultants,

Ltd. v. Hollister, Inc., 863 F.2d 867, 872 (Fed. Cir. 1988). Even grossly negligent failures to disclose material information are not sufficient to render an otherwise valid patent unenforceable. Id. at 876.

In ascertaining intent, the court must consider the totality of the circumstances. Id. This includes any evidence of good faith, which militates against a finding of intent to deceive. Id.

"Intent need not, and rarely can, be proven by direct evidence." See Merck & Co., Inc. v. Danbury Pharmacal, Inc., 873 F.2d 1418, 1422 (Fed. Cir. 1989). Instead, an intent to deceive may be inferred from a failure to credibly explain a "*knowing* failure to disclose material information." Bruno Indep. Living Aids, Inc. v. Acorn Mobility Servs., Ltd., 394 F.3d 1348, 1354 (Fed. Cir. 2005) (emphasis added).

1. Dr. Paul Janssen

With respect to patents in which he was not an inventor – such as the '663 patent – Dr. Janssen's role was simply to request the Janssen patent department to begin preparing applications when the scientific research had reached the appropriate point. Dellenbaugh Tr. 106:1-7. He was not involved in the prosecution of patents filed on behalf of Janssen in the United States. Dellenbaugh Tr. 105:22-25, 106:8-11.

Nor is there any reason to believe that Dr. Janssen ever reviewed the application for the '663 patent, the prosecution history or the references that were disclosed to the Patent Office. Those activities fell outside the scope of Dr. Janssen's responsibilities and his normal practices at the time. Dellenbaugh Tr. 106:12-22.

Because Dr. Janssen was not substantively involved in the prosecution of the '663 patent, he had no disclosure obligations imposed on him by the United States Patent Office and could not have committed inequitable conduct. 37 C.F.R. § 1.56(a) (1985) (only inventors, prosecuting attorneys, or people substantively involved in the prosecution owe a duty of candor to the PTO).[18]

2. Dr. Frans Awouters

Second, Mylan accuses Dr. Awouters,[19] who, as mentioned above, submitted a declaration to the PTO regarding the characteristics of the compound ketanserin. PX 2 at 195-197.

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[18] See, e.g., Schreiber Foods, Inc. v. Beatrice Cheese, Inc. 92 F. Supp. 2d 857, 872, fn. 16 (E.D. Wis. 2000), rev'd on other grounds, 31 Fed. Appx. 727 (Fed Cir. 2002) ("Any attempt by an alleged infringer to conflate an opponent's corporate actors with the opponent's applicant group represents a distortion of the patent law, and also signals to a court that clear and convincing evidence of materiality and intent may be lacking.").

[19] Dr. Awouters is a retired Janssen employee who was medically unable to participate in the trial. Declaration of Dr. Denis Wuyts dated June 19, 2006.

Mylan faults Dr. Awouters for not volunteering information about pirenperone. Under the circumstances–a rejection concerning ketanserin–there was no need whatsoever for him to do so. Dellenbaugh Tr. 136:19-23. There is no proof – let alone clear and convincing proof – that Dr. Awouters knew anything about the prosecution of the '663 patent other than the submission of his declaration. In particular, there is no proof that he ever saw the prosecution history (other than the '517 application itself, PX 2 at 4-28, which later published as the '663 patent) or the references that were cited, or knew whether information about pirenperone was, or was not, either submitted or material. Dellenbaugh Tr. 135:9-136:7. All his declaration states is that he had read "the specification and claims of U.S. patent Application Serial No. 826,517 and fully underst[ood] the contents thereof." PX 2 at 176.

The undisputed evidence shows that in the normal course, Dr. Awouters would have not been shown any other information. When a declaration was needed from a non-inventor to support a technical point, it was the normal practice of Dellenbaugh and the Janssen patent department simply to explain to the declarant the objection raised by the PTO and to ask whether there was any evidence that would help to disprove it. Dellenbaugh Tr. 133:17-134:7. There was no reason to show the scientist all of the unrelated communications with the

PTO or the prior art that had been submitted during prosecution. There was certainly no reason to discuss with the declarant a reference the examiner had not relied upon. Dellenbaugh Tr. 134:8-135:8.

The only obligation that Dr. Awouters assumed was to submit a truthful declaration. 37 C.F.R. 1.56(a) (1985) (the duty to the PTO is "commensurate with the degree of involvement in the preparation or prosecution of the application"). This he did, swearing to its truthfulness, and the accuracy of his declaration is unchallenged. PX 2 at 197. There is no evidence – let alone clear and convincing evidence – that Dr. Awouters ever was in a position to assess whether pirenperone data was even relevant to the prosecution of the patent, let alone that he formed an intent to deceive the PTO about such information. Without such knowledge, Dr. Awouters could not form an intent to deceive the PTO.

3. <u>Geoffrey Dellenbaugh</u>

Finally, Mylan accuses Dellenbaugh of harboring an intent to deceive. Dellenbaugh testified that he relied on Janssen counsel in Europe to prepare the application and that he had no reason to doubt the veracity or completeness of any statement contained therein. Dellenbaugh Tr. 107:16-108:2, 108:18-21, 117:12-118:11.

There is no evidence that he knew that pirenperone was a dopamine

antagonist.[20]

"[T]here can not have been culpable intent in withholding information that the inventor did not have." Herbert v. Lisle Corp., 99 F.3d 1109, 1115-16 (Fed. Cir. 1996) (quoting Therma-Tru Corp. v. Peachtree Doors, Inc., 44 F.3d 988, 996 (Fed. Cir. 1995)).

While there is no evidence of an intent to deceive, there is affirmative

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[20] Dellenbaugh testified that he had no knowledge of the references Mylan alleges were withheld from the PTO. Dellenbaugh Tr. 144:22-25 (no knowledge of DX 86), 145:19-146:3 (no knowledge of DX 89); 147:18-20 (no knowledge of DX 112), 149:2-8 (no knowledge of DX 120), 153:7-10 (no knowledge of DX 116), 193:14-194:6 (no knowledge of DX 203).

Mr. Dellenbaugh did not have any discussions with any the authors of these references, including Dr. Awouters, Kennis, Dr. Janssen and Dr. Gelders, about dopamine activity of pirenperone. Dellenbaugh Tr. 154:14-25.

Dellenbaugh had no recollection of meeting with or talking to Kennis, Dr. Awouters or Dr. Janssen during the time period the '663 patent was prosecuted and it would have been contrary to his normal practice to have done so. Dellenbaugh Tr. 109:8-19, 117:8-11; 105:22-25.

Mr. Dellenbaugh had no knowledge of whether pirenperone was an antipsychotic, was a dopamine antagonist or passed apomorphine tests. Dellenbaugh Tr. 114:12-20. Nor was he likely to have learned of that information since he did not follow the literature or Janssen's research. Dellenbaugh Tr. 108:22-109:4.

Mr. Dellenbaugh's knowledge of pirenperone was based solely on the pirenperone patent itself, which contained no information about dopamine antagonism, apomorphine tests, and antipsychotic ability. PX 80; Dellenbaugh Tr. 113:3-14. Had he been aware of any of that information, he testified that he would have included it in the pirenperone's patent application. Dellenbaugh Tr. 112:3-23.

evidence of Dellenbaugh's good faith. Kingsdown, 863 F.2d at 876 (evidence of good faith must be considered). Most notably, Dellenbaugh cited the examiner to the setoperone patent – the closest prior art. During the prosecution of the '663 patent, Mr. Dellenbaugh expressly disclosed the '451 patent, which describes setoperone and includes both its dopamine and serotonin antagonism. He discussed the setoperone '451 patent in the '663 patent as well. PX 1 at 8:20-29. If Dellenbaugh or other Janssen employees were seeking to conceal from the PTO that prior art Janssen patents described antipsychotic compounds with dopamine and serotonin antagonism, the setoperone patent would never have been disclosed. Yet the setoperone patent was disclosed and it prompted no comments from the PTO.

C. **Balancing**

Had Mylan proved both materiality and intent, the Court would then balance the degree of materiality and degree of intent to make an equitable judgment as to whether the conduct was so culpable that the patent should be barred from enforcement. See Life Techs., 224 F.3d at 1324. Mylan, however, has failed to carry its burden. Thus, the '663 patent is not unenforceable for inequitable conduct.

V. Conclusion

For the foregoing reasons, the Court finds that Mylan and DRL have failed to prove by clear and convincing evidence that the '663 patent is obvious or that Janssen engaged in inequitable conduct. Thus, the '663 patent is neither invalid nor unenforceable, and as a result, Mylan and DRL have infringed that patent under 35 U.S.C. § 271(e)(2).

/s/ John C. Lifland, U.S.D.J.

Dated: October 13, 2006